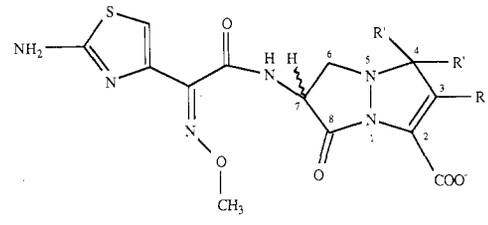
The Acylating Potential of γ-Lactam Antibacterials: Base Hydrolysis of Bicyclic Pyrazolidinones

Joseph M. Indelicato* and Carol E. Pasini

The Lilly Research Laboratories, Indianapolis, Indiana 46285. *Received October 9, 1987*

The acylating ability of the γ-lactam ring of a new class of antibacterial agent, the bicyclic pyrazolidinones 1, was compared to that of the β-lactam ring of clinically useful antibiotics by measuring chemical reactivity with hydroxide ion. The pyrazolidinone chemical reactivity spans the reactivity of classical β-lactam antibiotics and the most reactive, 1i, is 13 times more reactive than the most reactive β-lactam examined, ceftazidime. A correlation involving chemical reactivity, microbiological activity, and 3-substituent σ_p values was observed, and the correlation has led to the synthesis of new more potent bicyclic pyrazolidinones.

β-Lactam antibiotics act by binding to and inhibiting the action of various transpeptidase/carboxypeptidase enzymes involved in the synthesis of cell wall peptidoglycan.[1] A "fit" at the active site of the enzyme and a reactive β-lactam ring are both necessary for acylation and inhibition of these enzymes. An interesting exception to this rule is the naturally occurring non-β-lactam antibiotic, lactivicin, which has been reported to possess high affinity for the penicillin-binding proteins.[2] In the hope of discovering new classes of antibiotics, several groups have recently reported on the synthesis and antimicrobial activity of compounds in which the β-lactam ring has been replaced by a chemically activated γ-lactam ring.[3-11] For each class of lactam antibiotic there may be some minimum chemical reactivity necessary for microbiological activity dependent upon the quality of "fit" of that class at the enzyme's active site. We now report the acylating ability of the bicyclic pyrazolidinones[6-11] 1 and compare this reactivity with classical β-lactam antibiotics by measuring relative reactivity with hydroxide ion. This is of interest because the mechanism by which these antibacterials inhibit bacteria may be similar to that of classical β-lactams.[12] If correlations involving chemical reactivity, microbiological activity, and substituent constant values can be demonstrated, then the correlations may lead to the synthesis of new, more potent bicyclic pyrazolidinones.



1

Compound	R	R'
1a	$COCH_3$	H
1b	CO_2CH_3	H
1c	$CONHC_6H_5$	H
1d	CO_2^-	H
1e	2-Thiophene	H
1f	C_6H_5	H
1g	CO_2CH_3	CH_3
1h	CO_2^-	CH_3
1i	CN	H
1j	SO_2CH_3	H

Results and Discussion

Determination of the Rate Constants of γ-Lactam Hydrolysis by Titration, UV, and HPLC Methods. The acylating ability of β-lactam antibiotics has been determined by measuring the relative chemical reactivity of the β-lactam ring with hydroxide ion.[13] The reactivity of the γ-lactam ring of the bicyclic pyrazolidinones may be studied by similar experimental methods. An early technique to study the hydrolysis of penicillins was to measure the amount of hydroxide ion needed to titrate the penicilloic acid formed as the β-lactam was opened.[14] It

(1) Waxman, D. J.; Strominger, J. L. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 3, p 209.

(2) Harada, S.; Tsubotani, S.; Okazaki, H. *Tetrahedron Lett.* **1986**, *27*, 6229. Nozaki, S.; Katayama, H.; Ono, S.; Tsubotani, S.; Harada, S.; Okazaki, H.; Nakao, Y.; *Nature (London)* **1987**, *325*, 179.

(3) Boyd, D. B.; Elzey, T. K.; Hatfield, L. D.; Kinnick, M. D.; Morin, J. M. *Tetrahedron Lett.* **1986**, *27*, 3452.

(4) Boyd, D. B.; Foster, B. J.; Hatfield, L. D.; Hornback, W. J.; Jones, N. D.; Munroe, J. E. *Tetrahedron Lett.* **1986**, *27*, 3457.

(5) Baldwin, J. E.; Lowe, C.; Schofield, C. J. *Tetrahedron Lett.* **1986**, *27*, 3461.

(6) Jungheim, L. N.; Sigmund, S. K.; Fisher, J. W. *Tetrahedron Lett.* **1987**, *28*, 285.

(7) Jungheim, L. N.; Sigmund, S. K.; Jones, N. D.; Swartzendruber, J. K. *Tetrahedron Lett.* **1987**, *28*, 289.

(8) Jungheim, L. N.; Sigmund, S. K. *J. Org. Chem.* **1987**, *52*, 4007.

(9) Jungheim, L. N.; Sigmund, S. K.; Holmes, R. E.; Barnett, C. J.; Ternansky, R. J.; Eur. Pat. Appl. EP 202 046, U.S. Appl. 729 021.

(10) Ternansky, R. J.; Draheim, S. E. *The Synthesis of Bicyclic Pyrazolidinone Antibacterial Agents*; Abstract Number T-17, 30th National Organic Symposium, Vancouver, Canada, 1987.

(11) Ternansky, R. J.; Draheim, S. E.; Pike, A. J.; Ott, J. L. *Pyrazolidinone Antimicrobial Agents. Synthesis and In Vitro Activity of New Highly Potent Analogues*; Abstract Number 1213, XXVII Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), New York, NY, 1987.

(12) (a) Hobbs, J. N.; Andonov-Roland, M. M.; Allen, N. E. *Inhibition of Peptidoglycan Biosynthesis by LY 186826*; Abstract Number 604, XXVI Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), New Orleans, LA, 1986 (LY 186826 is 1a and both binds to PBPs as well as inhibits peptidoglycan biosynthesis). (b) Boyd, D. B. In *Frontiers in Antibiotic Research*; Umezawa, H., Ed.; Academic: Tokyo, 1987; p 339.

(13) (a) Indelicato, J. M.; Norvilas, T. T.; Pfeiffer, R. R.; Wheeler, W. J.; Wilham, W. L. *J. Med. Chem.* **1974**, *17*, 523. (b) Yamana, T.; Tsuji, A.; Kanayama, K.; Nakano, O. *J. Antibiot.* **1974**, *27*, 1000. (c) Yamana, T.; Tsuji, A. *J. Pharm. Sci.* **1976**, *65*, 1563. (d) Boyd, D. B. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 1, p 437. (e) Page, M. I. *Acc. Chem. Res.* **1984**, *17*, 144. (f) Boyd, D. B.; Eigenbrot, C.; Indelicato, J. M.; Miller, M. J.; Pasini, C. E.; Woulfe, S. R. *J. Med. Chem.* **1987**, *40*, 528. (g) Indelicato, J. M.; Fisher, J. W.; Pasini, C. E. *J. Pharm. Sci.* **1986**, *75*, 304.

0022-2623/88/1831-1227$01.50/0

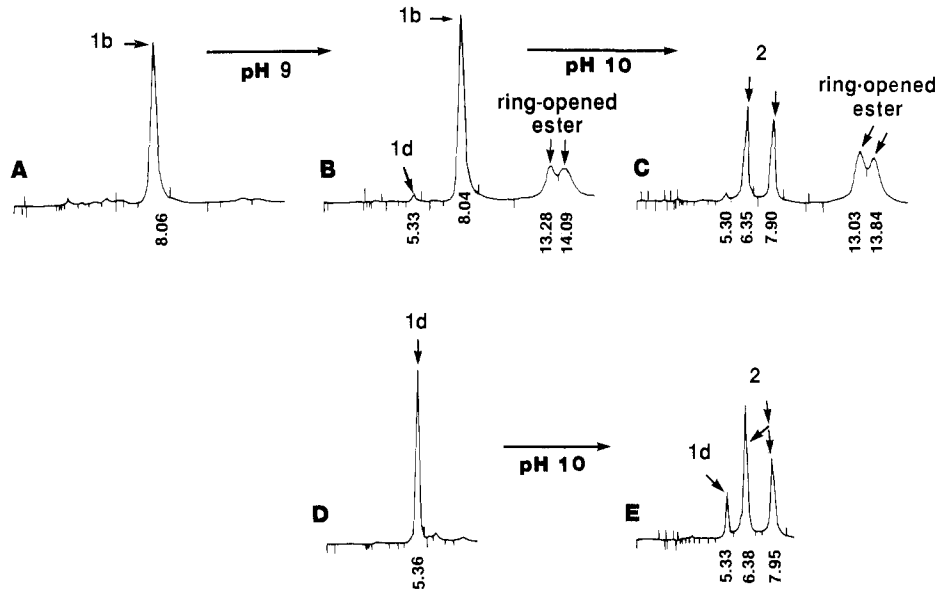
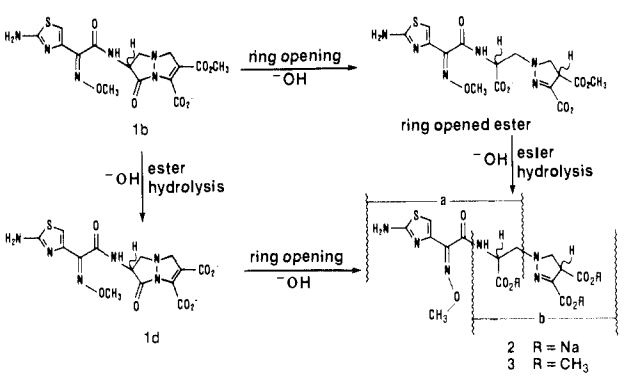


Figure 1. Sequential HPLC chromatograms of **1b**: (A) unreacted solution, (B) after ~40% reaction at pH 9, (C) after disappearance of **1b**, reaction solution was raised to pH 10. Sequential HPLC chromatograms of **1d**: (D) unreacted solution, (E) after ~75% reaction at pH 10. The secondary product, **2**, formed from the sequential hydrolysis of **1b** is identical with the hydrolysis product of **1d**.

is assumed with this method that the penicillin sample is pure and that no subsequent reactions occur that produce acid or base. The early technique to study the hydrolysis of cephalosporins was to follow the loss of the UV chromophore at ~260 nm associated with the intact cephalosporin nucleus.[13a,15] It is assumed with this method that the cephalosporin sample is pure and that the products from other chemical reactions or reactions subsequent to ring opening do not interfere with the measurement at ~260 nm. The advantage of the titration and the UV methods is that each measures a change in a single functionality, the β-lactam ring, in polyfunctional molecules. The preferred kinetic method for studying the hydrolysis of β-lactams is to follow their loss from solution by HPLC.[13c] This method is accurate, does not require pure compound, and requires only milligrams of material. However, the method does not indicate which functional group (in cases where hydrolysis may occur at more than one functional group) is reacting and therefore requires an independent product study that does require larger amounts of material.

We have applied all three experimental rate methods (titration, UV, and HPLC) to study the hydrolysis of bicyclic pyrazolidinone **1b**. The experimental data obtained by following the loss of parent compound, by HPLC (for 2–3 half-lives), resulted in a straight line when plotted as a pseudo-first-order reaction. The data obtained by the UV and titration methods also resulted in straight-line plots but with considerably more scatter in the data. However, all three methods resulted in essentially the same rate constant, 0.17 h^{-1} (HPLC), 0.19 h^{-1} (titration), or 0.21 h^{-1} (UV) at pH 9, 35 °C, presumably for the hydrolysis of the γ-lactam ring. These rates were determined in water to simplify isolation of the hydrolysis products subsequent to the titration experiment. All other rate constants in this study were determined in aqueous potassium chloride solution at a constant ionic strength of $\mu = 0.5$ [where the rate constant for the hydrolysis of **1b** at pH 9 is ~2.8 times faster, or 0.474 ± 0.015 h^{-1} (HPLC)] and converted to a rate constant at pH 10 (Table I) by assuming k_{obsd} is directly proportional to [$^-$OH].

Scheme I



While it is reassuring that all three methods result in approximately the same rate constant, this does not prove that the methods measure only the hydrolysis of the γ-lactam ring. There are two possible sites for hydrolysis in **1b**, i.e., at the γ-lactam ring and at the methyl ester (see Scheme I), and the possibility exists that some other reaction could be occurring with this unstudied class of compounds. Indeed, HPLC chromatograms of a partially hydrolyzed reaction solution of **1b** have demonstrated the possibility of sequential reactions. Subsequent isolation and identification of the final hydrolysis product confirmed a stepwise hydrolysis of first the γ-lactam ring and second the methyl ester. In Figure 1 the HPLC chromatograms of a reaction solution of **1b** at pH 9 show the appearance of two primary product peaks (diastereomers, a result of the introduction of asymmetry at C_3 in the product) due to opening of the γ-lactam ring. Only trace levels of the γ-lactam ring intact diacid **1d** are observed. Increasing the pH of the reaction solution from 9 to 10 results in the disappearance of these initial product peaks and the appearance of two secondary product peaks (ring-opened diastereomers of **1d**). In a parallel experiment **1d** was found to be relatively stable at pH 9 but to undergo γ-lactam ring opening at pH 10. The ring-opened product was chromatographically identical with the second product formed from the sequential hydrolyses of **1b**. Therefore, for **1b** where loss of parent compound as measured by

(14) Kinget, R. D.; Schwartz, M. A. *J. Pharm. Sci.* **1968**, *58*, 1102.
(15) Sabath, L. D.; Jago, M.; Abraham, E. P. *J. Biochem.* **1965**, *96*, 739.
(16) Yamana, T.; Tsuji, A. *J. Pharm. Sci.* **1976**, *65*, 1563.

Table I. Qualitative Correlation between Pseudo-First-Order Rate Constants, k (HPLC), for the Hydrolysis of the γ-Lactam Ring of Bicyclic Pyrazolidinones at pH 10, μ = 0.5, 35 °C, and Microbiological Activity (Agar Dilution MIC's, μg/mL)[j]

			MIC, μg/mL		
compd	k, h^{-1}	compd ref	*Streptococcus pyrogene* C203	*Klebsiella pneumoniae* X68	*Providencia rettgeri* C24
1i	(17.3 ± 1.6)[a,i]	*c*	0.5	0.5	0.25
1j	(14.8 ± 0.6)[a]	*c, d*	0.25	0.25	0.06
1a	(7.24 ± 0.40)[a]	*e*	0.5	2	0.25
1b	(4.74 ± 0.15)[a]	*f*	4	8	1
1c	(2.33 ± 0.17)[a]	*e*	1	32	8
1g	0.769 ± 0.058	*g*	64	>128	>128
1d	0.324 ± 0.010	*f*	8	64	8
1e	0.190 ± 0.020	*h*	>128	>128	>128
1f	0.146 ± 0.006	*h*	>128	>128	>128
1h	(0.0111 ± 0.0014)[b]	*g*	>128	>128	>128

[a] Experimentally measured at pH 9 and calculated as 10 times the observed rate constant assuming K_{obsd} is directly proportional to [$^-$OH]. [b] Experimentally measured at pH 11 and calculated as $^1/_{10}$ the observed rate constant assuming K_{obsd} is directly proportional to [$^-$OH]. [c] Reference 9. [d] Reference 10. [e] Reference 7. [f] Reference 6. [g] Reference 5. [h] Reference 8. [i] Rate constant was determined on pure *S* isomer. All other rate constants in Table II were determined on racemic (*RS*) compounds. All MIC data are for racemic bicyclic pyrazolidinones including **1i**. However, studies with *R* and *S* isomers of **1b** (supplied by R. E. Holmes) showed no significant differences in rate constant from the (*RS*) mixture: (*R*)-**1b** = 4.39 ± 0.08 h^{-1}; (*S*)-**1b** = 4.22 ± 0.26 h^{-1}. [j] The bicyclic pyrazolidinones included in this report are active in vitro against nonenterococcal streptococci, *Haemophilus influenzae*, and most species within the family *Enterobacteriacae*. These agents are only moderately active against the staphylococci and *Bacteroides fragilis*, and ineffective against *Pseudomonas aeruginosa*.

HPLC could be due to hydrolysis either at the ester moiety or at the γ-lactam ring, we believe that the HPLC-measured rate constant at pH 9 is primarily for the hydrolysis of the γ-lactam ring. (An analogous sequential hydrolysis was observed for **1g**.) We presume that the HPLC rate constants reported for the other bicyclic pyrazolidinones are for the hydrolysis of their γ-lactam ring.

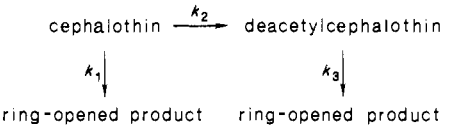
Identification of Diastereomeric Hydrolysis Product 2. The fast atom bombardment (FAB) mass spectrum of the product formed from the sequential hydrolyses of **1b** was consistent with the structure of diastereomeric trisodium salt **2**. However, MS (FAB) studies on diastereomeric trimethyl ester **3** obtained by reaction of the tricarboxylic acid of **2** with diazomethane were more useful in establishing its structure. Exact mass determinations on the parent (M + H) peak, fragment **3a** (m/z and m/z + H) peaks, and fragment **3b** (m/z) peak showed good agreement between experimentally determined and calculated molecular weights and confirmed the structure of **2**.

The ^{1}H NMR spectrum was also consistent with structure **2**. Some peaks were doubled due to the presence of diastereomers. The site of protonation after γ-lactam ring opening was found to be C_3 by ^{13}C NMR spectroscopy. The distortionless enhancement by polarization transfer (DEPT) spectra showed three doublet and eight singlet carbon resonances. Protonation on N_1 would have resulted in two doublet and nine singlet carbon resonances. Protonation on C_3 creates a second stereogenic carbon and accounts for the doubling of peaks in the NMR spectra and HPLC chromatograms.

Table II. Pseudo-First-Order Rate Constants for the Hydrolysis of the β-Lactam Ring of Cephalosporins, a Penicillin, and a Monobactam at pH 10, μ = 0.5, 35 °C

compd	k, h^{-1}	compd	k, h^{-1}
ceftazidime	1.30 ± 0.09	cephalexin	0.0685 ± 0.0034
cefaclor	0.944 ± 0.074	aztreonam	0.40 ± 0.03[b]
cephalothin, (hydrolysis β-lactam)	0.317[a]	penicillin V	0.248[c]

[a] There are two possible sites for hydrolysis in cephalothin, at the β-lactam ring and at the 3′-acetoxy ester moiety. At pH 10 reaction occurs at both sites and separation of the rate constants is not as straight foward as in the case of **1b**.



Experimentally we have measured the disappearance of cephalothin, k_{obsd} (where $k_{obsd} = k_1 + k_2$), by HPLC and in an independent experiment the disappearance of authentic deacetylcephalothin, k_3, also by HPLC. From these rate constants and from the experimental data points for the solution time courses for cephalothin and deacetylcephalothin (at pH 10, 35 °C, 0.1 M. carbonate, μ = 0.5). Dr. M. Pikal (Lilly Research Labs) has calculated for us the values of k_1 and k_2 with the MLAB software (National Institutes of Health): k_1 = 0.317 h^{-1}, k_2 = 0.485 h^{-1}, and k_3 = 0.158 h^{-1}. These rate constant values differ somewhat from the values in ref 16 where k_1–k_3 were calculated similarly by an analogue computer program without an experimentally determined value for k_3. [b] Rate constant from ref 13g. [c] Rate constant from ref 13a.

Relative Chemical Reactivity of the γ-Lactam Ring. The chemical reactivity of the bicyclic pyrazolidinone γ-lactam ring is influenced by the electronic effects of the 3-substituent (see Table I), reminiscent of the 3′-substituent effect on reactivity of the β-lactam ring of cephalosporins.[13a] The difference in reactivity between the most reactive (**1i**) and the least reactive (**1h**) bicyclic pyrazolidinone is approximately 1500-fold. The pyrazolidinone chemical reactivity spans the reactivity of classical β-lactam antibiotics (see Table II) and the most reactive, **1i**, is 13 times more reactive than the most reactive β-lactam, ceftazidime, examined in this study. The microbiologically active bicyclic pyrazolidinones thus possess the intrinsic chemical reactivity to acylate the penicillin binding proteins (PBPs)[12] and therefore mimic the action of classic β-lactam antibiotics.

Rate Constant Correlations. The pseudo-first-order rate constants of γ-lactam ring opening at pH 10, 35 °C, for 3-substituted bicyclic pyrazolidinones **1a–f** correlate with substituent constants σ_p (r = 0.98). The microbiological activity of these six bicyclic pyrazolidinones as well as the 4-dimethyl-substituted bicyclic pyrazolidinones **1g** and **1h** also correlate qualitatively with chemical reactivity (see Table II). Compound **1a** is the most microbiologically active, compounds **1b** and **1c** possess less activity, compounds **1d** and **1g** show only a trace of activity, and compounds **1e**, **1f**, and **1h** are inactive. If one assumes that the observed qualitative correlation between microbiological reactivity and γ-lactam ring reactivity is not a coincidence, then even more chemically reactive bicyclic pyrazolidinones may be expected to show more microbiological activity. Two more chemically reactive bicyclic pyrazolidinones, **1i** and **1j**, have recently been synthesized.[10,11] The pseudo-first-order rates of γ-lactam ring opening for these compounds also correlate as expected

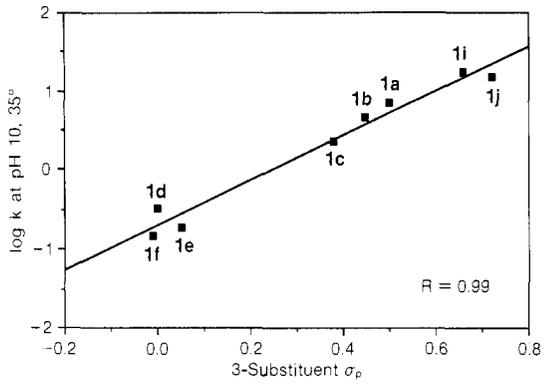


Figure 2. Correlation between pseudo-first-order rates of γ-lactam ring opening at pH 10, 35 °C, for 3-substituted bicyclic pyrazolidinones and the substituent constants σ_p (r = 0.99).

with the 3-substituent constants, σ_p (r = 0.99) (Figure 2) and have been found to be the most microbiologically active members of this series.

In conclusion, the hydrolysis rate of the γ-lactam ring of the bicyclic pyrazolidinones is as great or greater than that of the β-lactam of penicillins, cephalosporins, and the monobactam, aztreonam, and thus the bicyclic pyrazolidinones possess the intrinsic chemical reactivity needed to inhibit bacterial-wall synthesis by classic β-lactam mechanisms.[12] The 3-substituent influences the chemical reactivity of the γ-lactam ring, and the σ_p values for the 3-substituents correlate with the hydrolysis rate constants. An extrapolation of this correlation has led to the synthesis of more microbiologically active bicyclic pyrazolidinones.

Experimental Section

Lactams. The bicyclic pyrazolidinones used in this study were supplied by colleagues at Lilly Research Laboratories and synthesized by procedures referenced in Table I. The cephalosporins were from production lots of the commercial products. The ^{1}H NMR spectrum was obtained with a Bruker WM-270 spectrometer operated at 270.134 MHz (sodium 3-(trimethylsilyl)propionate-2,2,3,3,-d_4 was used as the external standard). The ^{13}C NMR spectra were obtained with a Bruker WM-250 spectrometer operated at 62.896 MHz (dioxane was used as the external standard). DEPT spectra were obtained by use of 90° and 135° pulses, which allowed the identification of the number of attached protons for all carbons. FAB mass spectra were determined on a Varian VG-ZAB-3F mass spectrometer (the samples were dissolved in a mixture of five parts dithiothreitol and one part dithioerythritol, "magic bullet").

Kinetic Methods. Titration. The pyrazolidinonic acid produced in the hydrolysis of **1b** at pH 9 was measured by constant pH titration (Schwartz method for the analogous penicillinoic acid[14]). The automatic titration was performed on a pH stat consisting of a Metrohm 655 dosimat, 614 implusomat, and a 632 pH meter fitted with a combination electrode. The γ-lactam concentration was 1.1×10^{-2} M. Carbon dioxide was excluded from the system with argon. The pH was maintained by the addition of NaOH. The pseudo-first-order rate constant was calculated from data obtained over 1 half-life. The pH of the reaction solution was then adjusted to pH 11, and the reaction solution was lyophilized the next day for the product study.

UV. The hydrolysis of **1b** was measured by a UV method described earlier for cephalosporins.[13a] The loss of the UV absorbance at 330 nm was followed for 2 half-lives with a Hitachi 100-80 spectrometer. The γ-lactam concentration was 6×10^{-4} M and the pH was maintained at 9 by the addition of NaOH on pH-stat system described above.

HPLC. The hydrolysis rates were determined by following the loss of parent lactam for 2 or more half-lives. The system consisted of a Beckman 332 chromatograph, a Rheodyne 7125 injection valve fitted with a 20-μL loop, a Waters 450 or a Kratos Spectroflow 773 detector, and a Hewlett-Packard 3390A integrator. The stationary phase was a 4.4 × 250 mM Zorbax ODS (Du Pont) reverse-phase column, and the detector was set at 254 nm. The flow rate was 1 mL/min. The mobile phases (v:v) were as follows. MeCN/0.5% H_3PO_4: **1a** (9:91), **1c** (25:75), **1e** (30:70), **1f** (30:70). MeOH/0.5% H_3PO_4: **1b** (20:80), **1d** (20:80), **1g** (34:66), **1h** (30:70), ceftazidime (25:75). MeCN/0.025 M $NH_4H_2PO_4$: **1i** (8:92), **1j** (7:93), cefaclor (10:90). MeOH/0.1 M NH_4OAc: cephalexin (35:65). MeOH/pH 5, 0.05 M acetate: cephalothin (35:65). All rates were determined at constant pH on the pH-stat system described above. The lactam concentrations were 3.6×10^{-4} to 1×10^{-3} M, and the pH was maintained at 9, 10, or 11 by the addition of NaOH. The ionic strength was adjusted to 0.5 with potassium chloride. The rate for **1b** was determined both at constant ionic strength and in pure water for comparison with the above titration and UV rates.

Identification of 2. An HPLC chromatogram of the solution from the above rate experiment (titration) contained only two peaks of equal area. Because we expected the formation of a diasteromic product, the mixture was characterized (after lyophilization) without further separation and was consistant with diastereomeric **2** trisodium salt: ^{1}H NMR (D_2O) δ 3.48, 3.53, 3.58, 3.64 (m, 4 H), 3.86, 3.89 (m, 1 H), 3.95, 3.96 (s, 3 H), 4.56, 4.65 (m, 1 H), 7.13, 7.14 (s, 1 H). DEPT ^{13}C NMR (D_2O) 8 s at δ 141.03, 149.79, (150.82 and 151.35), 164.93, 169.93, 171.75, (176.82 and 176.92), (179.56 and 179.68), 3 d at δ 63.6, (55.08 and 55.49), (115.08 and 115.15), 2 t at δ (56.61 and 56.80), (59.76 and 60.44), 1 q at δ 54.98. MS (FAB), (M + Na) m/z 517, (M + H) 495.

A portion of the lyophilized product was slurried in methanolic HCl, the precipitated NaCl was removed by filtration, and the solution was concentrated to an oil under vacuum. The oil was dissolved in methanol and treated with excess diazomethane in ether to give diastereomeric **3**, an oil, after vacuum removal of the solvent: MS (FAB), **3** (M + H) exact mass determination calcd for $C_{17}H_{23}N_6O_4S$ 471.1298, found 471.1298; **3a** (m/z) exact mass determination calcd for $C_{10}H_{13}N_4O_4S$ 285.0657, found 285.0666; **3a** (m/z + H) exact mass determination calcd for $C_{10}H_{14}N_4O_4S$ 286.0736, found 286.0744; and **3b** (m/z) exact mass determination calcd for $C_{11}H_{16}N_3O_6$ 286.1039, found 286.1032.

Acknowledgment. We gratefully acknowledge David A. Preston and Dr. John L. Ott for the microbiological data, John L. Occolowitz for the MS interpretations, Dr. Donald B. Boyd for use of his substituent parameter data base (created from the Pomona College Medchem Files), and Thomas K. Elzey and Dr. Ann Hunt for the NMR assignments. We also acknowledge Sue E. Draheim, Dr. Richard E. Homes, Dr. Louis N. Jungheim, David A. Neel, Sandra K. Sigmund, and Dr. Robert J. Ternansky for the gift of the bicyclic pyrazolidinones without which this study would have been impossible.